REMARKS

New claims 11-45 are pending in this application for the Examiner's review and consideration. Applicants have amended the specification and claims to conform with U.S. patent practice and to more clearly recite the invention. As no new matter has been added herein, these changes should be entered.

Respectfully submitted,

Paul E Dietz (45,627)

Date December 28, 2001

for Thomas G Rowan

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Appendix A

Changes to the Abstract

Please add the following abstract:

--A novel taxane derivative with anticancer activity, a process for its preparation and a process for the preparation of 14-β-hydroxy-1,14-carbonate-baccatine III and V derivatives 13-substituted by an isoserine residue.--

Appendix B

Changes to the Specification

The paragraph at page 1, line 1 is revised as follows:

--TECHNICAL FIELD

The present invention relates to a novel taxane useful as chemotherapeutic agent, the pharmaceutical compositions containing it and a process for the preparation of 14-ß-hydroxy-l, 14-carbonate-baccatine III and V derivatives, substituted at the 13 position by an isoserine residue.--

The paragraph at page 1, line 6 is revised as follows:

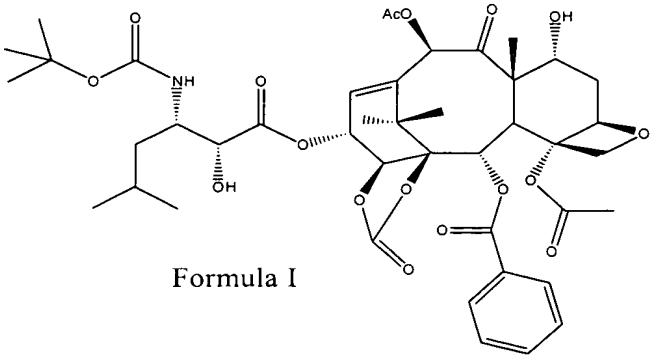
--BACKGROUND OF THE INVENTION

Taxanes are one of the most important classes of anticancer drugs recently developed. The remarkable effectiveness of Paclitaxel and of its analogue Docetaxel in the treatment of several tumors has focused research on substances with antimicrotubular activity. Taxanes are however characterized by a particular action mechanism, in that they promote the assembly of microtubules and inhibit tubuline depolymerization.--

The paragraph at page 1, line 31 is revised as follows:

--SUMMARY OF THE INVENTION

It has now been found that the compound of formula (I), a 14ß-hydroxy-l, 14-carbonate-baccatine V derivative,



Formula I

has remarkable cytotoxic and anticancer activities, and is capable of overcoming the resistance of cell lines expressing the MDR phenotype.--

The paragraph at page 2, line 14 is revised as follows:

--DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compound of the invention differs from the prior art derivatives due to the hydroxyl at the 7- position, which in the present case is in alfa configuration. 13-(N-Boc-ß-Isobutylisoserinyl) -14ß--hydroxy-baccatine III 1, 14-carbonate, corresponding to the derivative referred to in US 5,705,508 as SB-T-101131, can be used as starting product for the preparation of compound (I) . In this case, said baccatine III derivative is either treated with DBU (diazabicyclo[5,4,0] 7-undecene) in methanol or THF or it is simply left in solution with methylene chloride or chlorinated solvents in the presence of aliphatic alcohols such as methanol, ethanol or propanol with basic allumine for a time ranging from one hour to 14 days. The compound having beta configuration at C-7, is converted at neutral or slightly basic pH to the more stable alfa isomer (baccatine V derivative).--

The paragraph at page 28, line 1 is revised as follows:

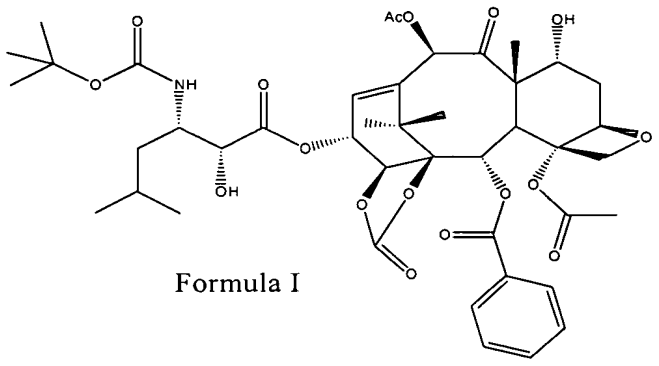
--CLAIMS

What is claimed is:--

Appendix C

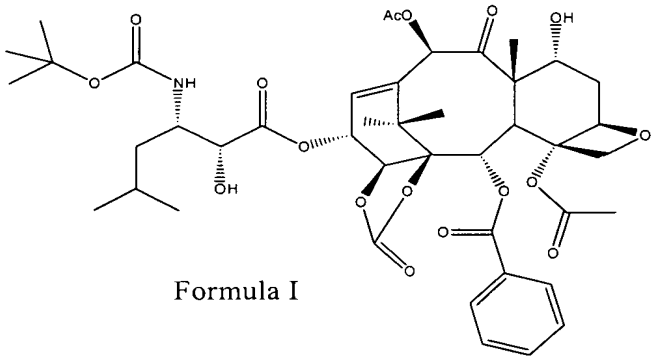
Currently Pending Claims

11. (New) A compound of Formula I.



Formula I

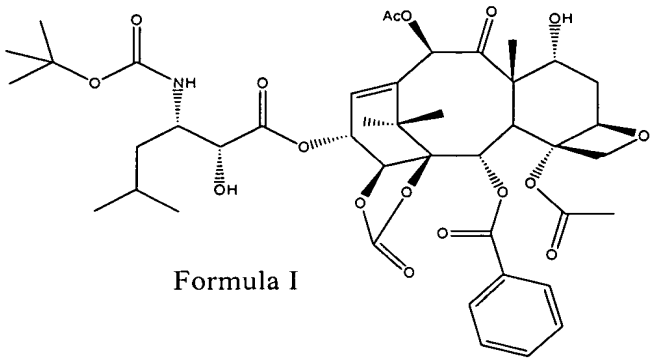
12. (New) A process for preparing a compound of Formula I,



Formula I

comprising reacting 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine III 1,14-carbonate with diazabicyclo[5,4,0] 7-undecene in methanol or THF.

13. (New) A process for preparing a compound of Formula I,



Formula I

comprising treating 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine III 1,14-carbonate with methylene chloride or chlorinated solvents in the presence of one or more aliphatic alcohols and basic allumine for from 1 hour to 14 days.

14. (New) The process of claim 13, wherein the one or more aliphatic alcohols are selected from methanol, ethanol, propanol, or a combination thereof.

15. (New) A process for preparing 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine III 1,14-carbonate or 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine V 1,14-carbonate, comprising:

a. reacting 14β-hydroxy-10-deacetylbaccatine III or 14β-hydroxy-10-deacetylbaccatine V with a silylating agent to provide a 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or a 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V;

b. reacting the 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or the 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V with phosgene to provide a 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or a 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V;

c. reacting the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V with a LiHMDS to provide a lithium salt of the 10-

hydroxyl group of the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or a lithium salt of 10-hydroxyl group of the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V;

d. reacting the lithium salt of the 10-hydroxyl group of the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or the lithium salt of the 10-hydroxyl group of the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V with an acetylating agent to acetylate the 10-hydroxyl group to provide a 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine III or a 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine V;

e. reacting the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine III or the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine V with (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid to form a C-13 esterified 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine III or a C-13 esterified 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine V; and

f. removing the 7-triethylsilyl group from the C-13 esterified 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine V to provide a C-13 esterified 1,14 carbonate 7-hydroxyl 14β-hydroxy-10-acetylbaccatine III or a C-13 esterified 1,14 carbonate 7-hydroxy 14β-hydroxy-10-acetylbaccatine V; and

g. removing a dimethoxybenzylidene group from the C-13 esterified 1,14 carbonate 7-hydroxyl 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 1,14 carbonate 7-hydroxy 14β-hydroxy-10-acetylbaccatine V

to provide 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine III 1,14-carbonate or 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine V 1,14-carbonate.

16. (New) The process of claim 15, wherein the silylating agent is triethyl chlorosilane.

17. (New) The process of claim 15, wherein the 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or the 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine

V is reacted with phosgene by dissolving the 7-triethylsilylated derivative in a methylene chloride/pyridine mixture in a 3:1 ratio and then adding a toluene solution containing phosgene to the methylene chloride/pyridine mixture under a nitrogen atmosphere.

18. (New) The process of claim 15, wherein the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V is reacted with LiHMDS in anhydrous THF.

19. (New) The process of claim 15, wherein lithium salt of the 10-hydroxyl group of the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine III or the lithium salt of the 10-hydroxyl group of the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-deacetylbaccatine V is acetylating with acetyl chloride.

20. (New) The process of claim 15, wherein the the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine III or the 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine V is reacted with the (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid in an anhydrous apolar organic solvent in the presence of a base and of a condensing agent.

21. (New) The process of claim 20, wherein the condensing agent is dicyclohexylcarbodiimide.

22. (New) The process of claim 15, wherein the 7-triethylsilyl group is removed from the 7-triethylsilyl group from the C-13 esterified 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 1,14 carbonate 7-triethylsilyl 14β-hydroxy-10-acetylbaccatine V with pyridinium fluoride in a acetonitrile/pyridine solution under nitrogen, and the dimethoxybenzylidene group is removed from the C-13 esterified 1,14 carbonate 7-hydroxyl 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 1,14 carbonate 7-hydroxy 14β-hydroxy-10-acetylbaccatine V in a methylene chloride solvent by addition of methanolic HCl followed by $NaHCO_3$.

23. (New) A process for preparing 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine III 1,14-carbonate or 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine V 1,14-carbonate, comprising:

a. acetylating the C-10 hydroxyl of 14β-hydroxy-10-deacetylbaccatine III or 14β-hydroxy-10-deacetylbaccatine V to provide 14β-hydroxy-10-acetylbaccatine III or 14β-hydroxy-10-acetylbaccatine V;

b. reacting the 14β-hydroxy-10-acetylbaccatine III or 14β-hydroxy-10-acetylbaccatine V with phosgene to provide a 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V;

c. silylating the C-7 hydroxyl of the 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V to provide a 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or a 7-silyl 1,14 carbonate derivative;

d. reacting the 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V with (4S,5R)-N-Boc-2- (2,4-dimethoxyphenyl) -4-isobutyl-l-oxazolidine-5- carboxylic acid to provide a C-13 esterified 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or a C-13 esterified 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V;

e. removing the 7-triethylsilyl group from the C-13 esterified 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V to provide a C-13 esterified 7-hydroxy 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or a C-13 esterified 7-hydroxy 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V; and

f. removing a dimethoxybenzylidene group from the C-13 esterified 7-hydroxy 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 7-hydroxy 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V

to provide 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine III 1,14-carbonate or 13-(N-Boc-β-isobutylisoserinyl)-14β-hydroxy-baccatine V 1,14-carbonate.

24. (New) The process of claim 23, wherein the C-10 hydroxyl of 14β-hydroxy-10-deacetylbaccatine III or 14β-hydroxy-10-deacetylbaccatine V is acetylated with acetic anhydride in the presence of cerium, scandium, and/or ytterbium salts.

25. (New) The process of claim 24, wherein the salt is $CeCl_3 \cdot H_2O$.

26. (New) The process of claim 23, wherein 14β-hydroxy-10-acetylbaccatine III or 14β-hydroxy-10-acetylbaccatine V is reacted with phosgene by dissolving the 14β-hydroxy-10-acetylbaccatine III or 14β-hydroxy-10-acetylbaccatine V in a methylene chloride/pyridine mixture in a 3:1 ratio and then adding a toluene solution containing phosgene to the methylene chloride/pyridine mixture under a nitrogen atmosphere.

27. (New) The process of claim 23, wherein the C-10 hydroxyl of 14β-hydroxy-10-deacetylbaccatine III or 14β-hydroxy-10-deacetylbaccatine V is acetylated with acetyl chloride.

28. (New) The process of claim 23, wherein the 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V is reacted with (4S,5R)-N-Boc-2- (2,4-dimethoxyphenyl) -4-isobutyl-l-oxazolidine-5- carboxylic acid is reacted with (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid in an anhydrous apolar organic solvent in the presence of a base and a condensing agent.

29. (New) The process of claim 28, wherein the condensing agent is dicyclohexylcarbodiimide.

30. (New) The process of claim 23, wherein the triethylsilyl protective group is removed from the the C-13 esterified 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 7-silyl 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V with pyridinium fluoride in a acetonitrile/pyridine solution

under nitrogen, and the dimethoxybenzylidene group is removed from the C-13 esterified 7-hydroxy 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine III or the C-13 esterified 7-hydroxy 1,14 carbonate derivative of 14β-hydroxy-10-acetylbaccatine V in a methylene chloride solvent by addition of methanolic HCl followed by $NaHCO_3$.

31. (New) A process for preparing (4S, 5R)-N-Boc-2-(2, 4-dimethoxyphenyl)-4- isobutyl-1-oxazolidine-5-carboxylic acid, comprising:

a. protecting an amino group of a leucinol with Boc to form N-Boc-L-leucinol;

b. converting of the N-Boc-L-leucinol into N-Boc-L-leucinal;

c. preparing a cyanhydrin nitrile from the N-Boc-L-leucinal;

d. transforming the cyanhydrine nitrile into a carboxylic acid;

e. forming of a methyl ester of the carboxylic acid from the carboxylic acid;

f. purifying the methyl ester of the carboxylic acid;

g. condensing the methyl ester of the carboxylic acid with 2,4-dimethoxybenzaldehyde dimethyl acetal to form (4S, 5R)-N-Boc-2-(2,4-dimethoxyphenyl) -4-isobutyl-l-oxazolidine-5-carboxylic acid methyl ester; and

h. transforming the (4S, 5R)-N-Boc-2-(2,4-dimethoxyphenyl) -4-isobutyl-l-oxazolidine-5-carboxylic acid methyl ester into the (4S, SR)-N-Boc-2-(2, 4-dimethoxyphenyl)-4- isobutyl-1-oxazolidine-5-carboxylic acid.

32. (New) A method of treating cancer in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of claim 1.

33. (New) The method of claim 32, wherein the compound is administered in an amount of from 50 to 500 mg/m^2.

34. (New) The compound 14β-hydroxy baccatine III.

35. (New) The compound 14β-hydroxy baccatine V.

36. (New) The compound 14β-hydroxy baccatine III 1,14 carbonate.

37. (New) The compound 14β-hydroxy baccatine V 1,14 carbonate.

38. (New) The compound 14-β-hydroxy-7-Tes-10-deacetylbaccatine III.

39. (New) The compound 14-β-hydroxy-7-Tes-10-deacetylbaccatine V.

40. (New) The compound 14-β-hydroxy-7-Tes-baccatine III.

41. (New) The compound 14-β-hydroxy-7-Tes-baccatine V.

42. (New) The compound 14-β-hydroxy-7-Tes-baccatine III 1,14-carbonate.

43. (New) The compound 14-β-hydroxy-7-Tes-baccatine V 1,14-carbonate.

44. (New) The compound (4S,5R)-N-Boc-2- (2,4-dimethoxyphenyl) -4-isobutyl-1-oxazolidine-5-carboxylic acid.

45. (New) A pharmaceutical composition comprising the compound of claim 1 and one or more pharmaceutically acceptable carriers and/or excipients.